REMARKS

Claims 14, 17-22 and 35 were pending in the instant application. Claims 14, 18, 20-22 and 35 have been amended. New claims 36-42 have been added. Support for the claim amendments and new claims can be found throughout the claims and specification as originally filed. In particular, support for new claims 37-42 can be found in the specification at page 3, lines 1-12. Claims 14, 17-22, and 35-42 will be pending after entry of the instant amendment. Applicants reserve the right to prosecute the claims as originally filed in this or a continuing application.

Objections

The amendment filed August 12, 2002 (mailed by Applicants on August 5, 2002) and substitute sequence listing filed June 2, 2003 (mailed by Applicants on May 30, 2003) are objected to as allegedly introducing new matter. Applicants traverse. The Examiner fails to indicate any particular new matter introduced in the prior-filed sequence listings. Applicants indicated the support for all sequences in the substitute sequence listing in a prior Amendment and Response (mailed May 30, 2003). No matter has been added that goes beyond the scope of the application as filed.

For the Examiner's convenience, the following comments are provided regarding sequence listings submitted in the instant case. The instant application was filed without a Sequence Listing. In response to an Office Communication dated May 17, 2001, Applicants prior attorneys submitted a sequence listing on June 18, 2001 including 15 nucleotide and/or amino acid sequences, as follows:

SEQ ID NO:	**Sequence**	**Support**
1	*rde-1* genomic sequence	Figure 5A-C
2	*rde-1* cDNA sequence	Figure 6A-D

3	RDE-1 amino acid sequence	Figure 6A-D
4	*rde-4* cDNA sequence	Figure 10A-B
5	RDE-4 amino acid sequence	Figure 10A-B
6	ZWILLE (regions of homology with RDE-1)	Figure 4B
7	Sting (regions of homology with RDE-1)	Figure 4B
8	consensus sequence	Figure 11
9	F48F7.1 (regions of homology with RDE-1)	Figure 4B
10	eIF2C (regions of homology with RDE-1)	Figure 4B
11	X1RBPA (regions of homology with RDE-4)	Figure 11
12	HsPKR (regions of homology with RDE-4)	Figure 11
13	RDE-1 (internal portion)	Figure 4B
14	RDE-4 (internal portion)	Figure 11
15	consensus sequence	Figure 11

In the substitute sequence listing filed May 30, 2003, SEQ ID NO:15, was removed. A review of Figure 11 shows a single consensus sequence (SEQ ID NO:8), and three internal portion amino acid sequences (SEQ ID NOs: 11, 12 and 14) whereas the prior-filed sequence listing indicated two consensus sequences. Hence, the substitute sequence listing included 14 total sequences as compared to 15 sequences listed in the first-filed sequence listing.

Applicants further submit herewith a second substitute sequence listing. The substitute sequence listing submitted herewith corrects an error detected in SEQ ID NO:5. A review of Figure 10 shows that the RDE-4 amino acid sequence terminates with the C-terminal amino acids YDFTD. Nucleotides1156-1158 are a STOP codon. Residues 3' terminal to the STOP codon are non coding. Applicants prior attorneys

inadvertently included the STOP and residues 3' terminal to STOP in SEQ ID NO:5. No new matter has been added.

Should the Examiner maintain any objections to the sequence listing, it is requested that the alleged new matter be indicated.

Claim Rejections Under 35 USC 112

Claims 14, 17, 20-22 and 35 are rejected under 35 U.S.C. 112, first paragraph as allegedly failing to comply to the written description requirement. Applicants traverse. Claims 14, 20-22 and 35 have been amended. The claims have been amended to recite that the RNAi component is an RDE-1 polypeptide or homolog or RDE-4 polypeptide or homolog. Applicants reserve the right to prosecute the claims as originally-filed in this or a continuing application. It is Applicants' position that the claims, as amended, comply with the written description requirement.

The genera of RDE-1 polypeptides or homologs and RDE-4 polypeptides and homologs are extensively described in the specification at least in Example 6 and Figure 4. The RDE-1 gene family including known homologs is described and conserved structural features and/or regions are described and depicted in Figure 4. The genus of RDE-4 polypeptides, homologs and fragments is described in the specification at least in Example 11 and Figure 11. Known homologs are described and conserved structural motifs and/or regions are described and depicted in Figure 11. Methods of identifying additional RDE-1 or RDE-4 homologs are described at page 10, line 4 through page 12, line 11. Example 6 further describes assays to determine whether a RDE-1 or RDE-4 polypeptide retains the activity of RDE-1 or RDE-4, respectively. Example 12 describes assays to determine whether a RDE-1 or RDE-4 domain or fragment retains the activity of RDE-1 or RDE-4, respectively.

Contrary to the Examiner's assertions, the specification is replete with teachings as to the structural and functional characteristics of the claimed genera of polypeptides. In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 14, 17, 20-22 and 35 under 35 U.S.C. §112, first paragraph.

Rejection of Claims 14, 17-22 and 35 Under 35 U.S.C. 112

Claims 14, 17-22 and 35 have been rejected under 35 U.S.C. 112 as allegedly lacking enablement. In particular, the Examiner alleges that the specification does not provide enablement for inhibiting activity of a gene *in vivo*. Applicants traverse.

The Examiner cites several references for the proposition that the art is unpredictable. Certain of the references cited by the Examiner describe the PKR response in mammalian systems. Certain of the reference cited by the Examiner describe alleged obstacles to therapeutic delivery of dsRNA. Applicants first note that *in vivo* methodologies are applicable to a number of *in vivo* systems where the PKR response is not a consideration, for example, invertebrate systems and PKR-deficient systems. Applicants have further submitted evidence of means of counteracting the PKR response in PKR-proficient mammalian systems. Even in PKR proficient systems, it may not be necessary to eliminate the PKR response to benefit from the sequence-specific gene silencing methodologies of the claimed invention. The Examiner cites additional references for the proposition that the complete mechanism of RNAi is not yet known. The relevance of this is questioned as there is no requirement the complete mechanism of action of an agent be known to enable methods that feature administering such an agent to achieve a desired result. Additional references are cited for the proposition that administration of the agents of the invention is unpredictable and undue experimentation would be required to practice the invention as claimed. Applicants note, however, that the art and the specification are replete with teachings as to the administration of nucleic

acid-based agents (*e.g.*, liposome formulations, direct injection, etc). The Examiner recognizes that the level of skill in the art is high but concludes that other factors outweigh the high level of skill in the art. It Applicants' position that the high level of skill and predictability in the art is evidenced by the fact that RNAi has successfully been practiced in several mammalian systems as evidence, for example, by the Svoboda *et al.*, Wianny and Zernicka-Goetz and Billy *et al.* references already of record in this case. In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 14 and 17-22 under 35 U.S.C. §112, first paragraph.

Claim Interpretation and Rejections Under 35 USC § 102 and § 103

The Examiner has interpreted claim 14 as indicated in paragraph 11 of the instant Office Action. Claim 14 (and dependent claims 21, 22 and 35) have been rejected under § 102 in view of Fire *et al.* (1998) *Nature* 391:806-811 and dependent claim 20 has been rejected under § 103 in view of Fire *et al.* and Wheeler *et al.* USP 5,976,567 based on the Examiner's claim interpretation. Applicants respectfully assert that the claim interpretation is erroneous. Claim 14 features introducing an RNAi agent into a cell, the agent being prepared by incubating a dsRNA with an RNAi pathway component (*e.g.*, RDE-1, RDE-4, homologs of same, *etc.*). Preparation of RNAi agents is taught throughout the specification. In exemplary embodiments, RNAi agents can be prepared *in vitro* or in cells, for example, in which a RNAi pathway component has been activated (*e.g.*, *via* transgenesis of the pathway component), see, for example, page 28, lines 21-31. Claim 14 features preparation of RNAi agents *in vitro*. Claims 23-34, featuring preparation in a cell, have been restricted (and are withdrawn from consideration) as being directed to patentably distinct subject matter (see Office Action dated November 15, 2002). Applicants respectfully submit that the claim interpretation set forth in paragraph 11 of the instant Office Action is inconsistent with the meaning of the claim

and with the previous restriction of distinct subject matter. Applicants reserve the right to comment on the patentability of the restricted subject matter in view of the references cited in the instant Office Action should such references form the basis of any rejection in an appropriately filed divisional or continuing patent application. Applicants further submit that the rejections of claims 14, 20, 21, 22 and 35 are moot in view of a proper claim interpretation.

CONCLUSION

In view of the above amendments and remarks, it is believed that this application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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